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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/711,969	10/15/2004	Scott R. Breining	T103 1580.1	5968

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EXAMINER	
O'DELL, DAVID K	

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1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/711,969	BREINING ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,11,12,15,16,18,70 and 73-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *79* is/are allowed.

6)☒ Claim(s) *1,4,11,12,15,16,18,70 and 73-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4, 11, 12, 15, 16, 18, 70, 73-79 are pending in the current application. Claims , 4, 11, 12, 15, 16, 18, 70, 73-79 are under examination.

2. This application claims benefit of U.S. Provisional Application 60/511,697 filed October 15, 2003.

Response to Arguments

3. Applicant's arguments filed November 20, 2007 have been fully considered but they are not persuasive. The examiner apparently inadvertently withdrew claim 11, which the applicant correctly pointed out in the latest reply. This claim is under examination, and does not effect the nature of the pending rejections. It is noted that in the reply to the restriction requirement the applicant did not point this out:

> Atty. Dkt. No. T103 1580.1 (42565.0354.4)
> Appl. Serial No.: 10/711,969
>
> **Response to Restriction Requirement**
>
> The claims have been restricted to 46 separate groups.
>
> Group I, is directed to Claims 1-4, 8, 12, 13, and 15-18, wherein the claims are drawn to the compounds of Formulas I and II wherein the ring is a 2-(pyridin-3-yl)-7-azabicyclo[3.3.1]non-2-ene, 3-(pyridin-3-yl)-7-azabicyclo[3.3.1]non-2-ene or a 2-(pyridin-3-yl)-7-azabicyclo[3.3.1]nonane core.

The examiner took this election on good faith as correct. Nonetheless this claim is rejoined. The rejections under 35 U.S.C. 112 2nd paragraph are withdrawn in light of the amendments. The enablement rejection is maintained in part and withdrawn in part. With respect to the position isomers IA and IC, the examiner overlooked adequate support in the disclosure as pointed out by

the applicant, and hereby withdraws the enablement rejection for these position isomers. This was clearly an oversight on the examiner's part and apologizes for this clear error. However with respect to the rejection insofar as the long list of groups are concerned (which are only the various Z's) the rejection is maintained. The rejections for scope of enablement are maintained as the directions for the preparation and use of the compounds commensurate in scope with the claims has not been provided. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again vide infra). It would appear that the applicant is arguing that essentially any molecule can be made without undue experimentation. This is in fact not the situation in the chemical arts. As stated in a recent book on the subject:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural

> features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

The examiner (vide infra and in the previous action) serve to show the scope that is enabled by the specification, in terms of the compounds, and the teaching of the prior art. Thus applicant's position regarding the state of the art in organic synthesis is not in line with that of the scientific community. Moreover the examiner not only applied the rejection for how to make, but also how to use. The examiner clearly outlined the state of the art in pyridyl nAChR ligands as related to these substituents, several references were cited to support this position and no argument or evidence was put forth to rebut the how to use portion of the rejection. See In re Budnick, 537 F2d 535, 190 USPQ 422 (C.C.P.A. 1976)

"We are persuaded that the findings and reasons of the examiner and the board satisfy the burden of the Patent and Trademark Office of substantiating doubts concerning enablement and that the burden has shifted to appellant to show that his specification would, indeed, enable one skilled in the art to make the claimed compounds. In re Eynde, 480 F.2d 1364, 178 USPQ 470 (CCPA 1973); In re Fouche, 58 CCPA 1086, 439 F.2d 1237, 169 USPQ 429 (1971)..... **However, the record is barren of any showing that the claimed compounds would, in fact, be formed, and argument of counsel cannot take the place of evidence.** In re Schulze, 52 CCPA 1422, 346 F.2d 600, 145 USPQ 716 (1965); In re Cole, 51 CCPA 919, 326 F.2d 769, 140 USPQ 230 (1964)."

A recent ruling by the Federal circuit discusses enablement in the context of the automotive art, but there is little difference in the position of the court and the position of the examiner instant case, ATI v. BMW et. al. (Fed. Cir. 2007):

"We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007). In that case, the invention was a front-loading fluid injector system with a replaceable syringe capable of at 1373. We construed the asserted claims, as urged by the patentee, to include an injector with and without a pressure jacket. Although the specification clearly enabled an injector with a pressure jacket, we concluded that it did not enable an injector without such a jacket and that the claims were invalid for lack of enablement. at 1379. We stated that there "must be 'reasonable enablement of the scope of the range' which, in this case, includes both injector systems with and without a pressure jacket." withstanding high pressure for delivering a contrast agent to a patient. Id. Id. Id. at 1380 (internal citation omitted).
Similarly, in this case, the claim construction of the relevant claim limitation resulted in the scope of the claims including both mechanical and electronic side impact sensors. Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors. Electronic side impact sensors are not just another known species of a genus consisting of sensors, but are a distinctly different sensor compared with the well-enabled mechanical side impact sensor that is fully discussed in the specification. Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both electronic and mechanical side impact sensors, which the specification fails to do. We stated in Liebel: "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Id. at 1380. ATI sought to have the scope of the claims of the '253 patent include both mechanical and electronic side impact sensors. It succeeded, but then was unable to demonstrate that the claim was fully enabled. Claims must be enabled to correspond to their scope."

The very limited disclosure and the inordinate amount of experimentation required to practice the invention, clearly warrant the conclusion made by the examiner, which was supported by references testifying to the state of the art and its unpredictability. Claim 79 is allowed. This action is made FINAL.

I. Claims 1-4, 8, 11, 12, 13, 15-18, 70 drawn to compounds where in either Formula I or Formula II of claim 1, k=1, p=1, Ar is 3-pyridyl, and if m is 1 then n is 0 or if n is 1 m is 0, drawn to compounds and compositions having either a 2-(pyridin-3-yl)-7-azabicyclo[3.3.1]non-2-ene core **IA**, or a 3-(pyridin-3-yl)-7-azabicyclo[3.3.1]non-2-ene core **IB**, or a 2-(pyridin-3-yl)-7-azabicyclo[3.3.1]nonane core **IC** or a 3-(pyridin-3-yl)-7-azabicyclo[3.3.1]nonane core **ID** as shown in Figure 1, classified in class 540, subclass 477.

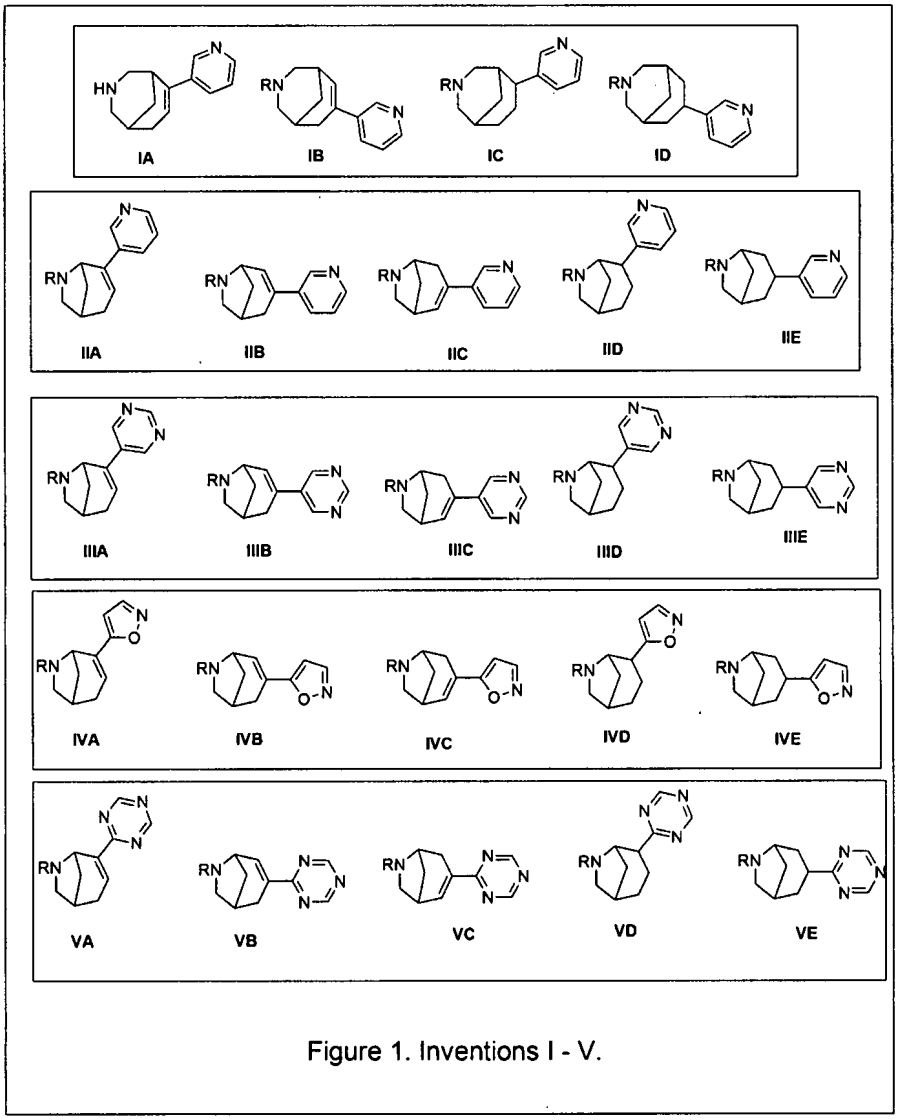


Figure 1. Inventions I - V.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4, 12, 13, 15-18, 70, 73-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The compounds that are enabled for synthesis are as follows:

Zj where j is zero (in terms of the azabicyclo ring system), m is 1, n is 0, k=1, p=1, the Z of the 3-pyridinyl moiety should be limited to lower alkyl, amino, halogen, OH, alkoxy. R has been amended.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

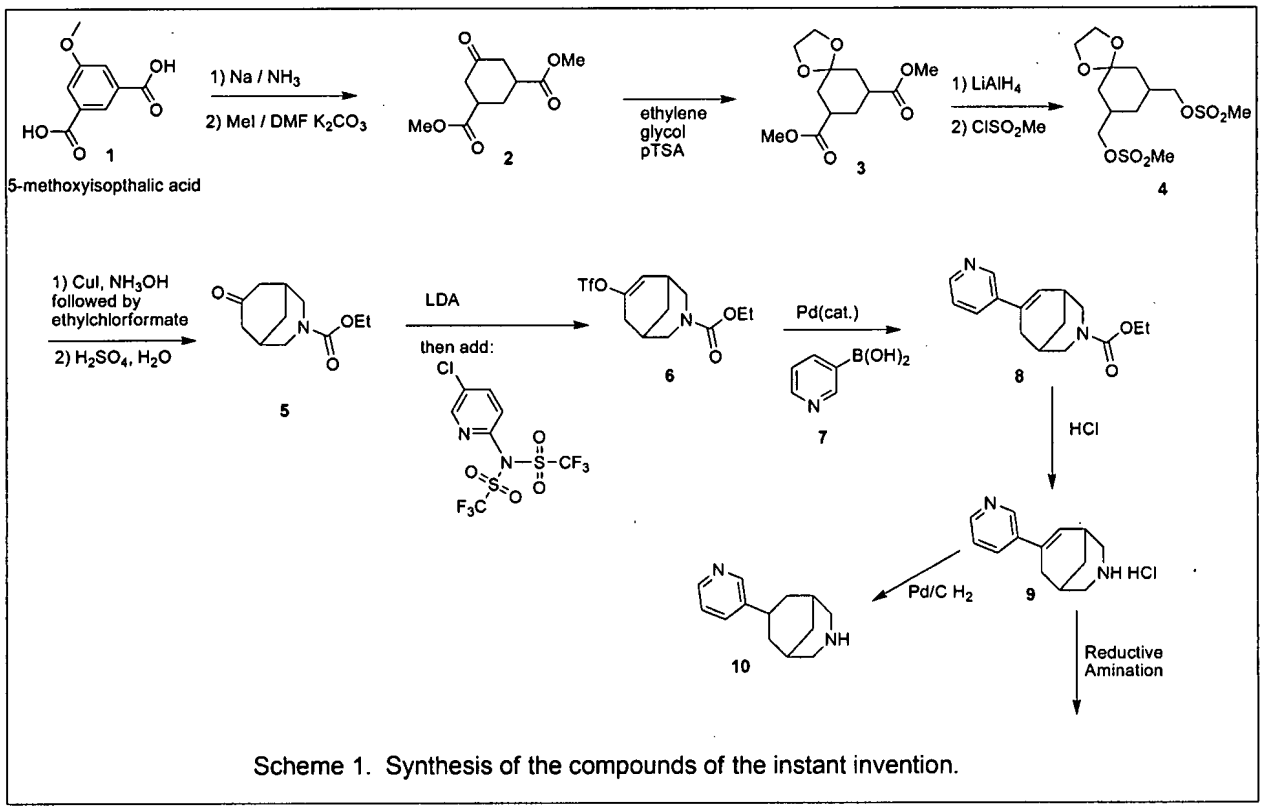
(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, carbocycles and other groups bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at nAChAr. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. Little prior art exists on these

compounds, however they will be evaluated on what is known using scientific principles. Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C, E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structures I and II of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples.

As per MPEP:

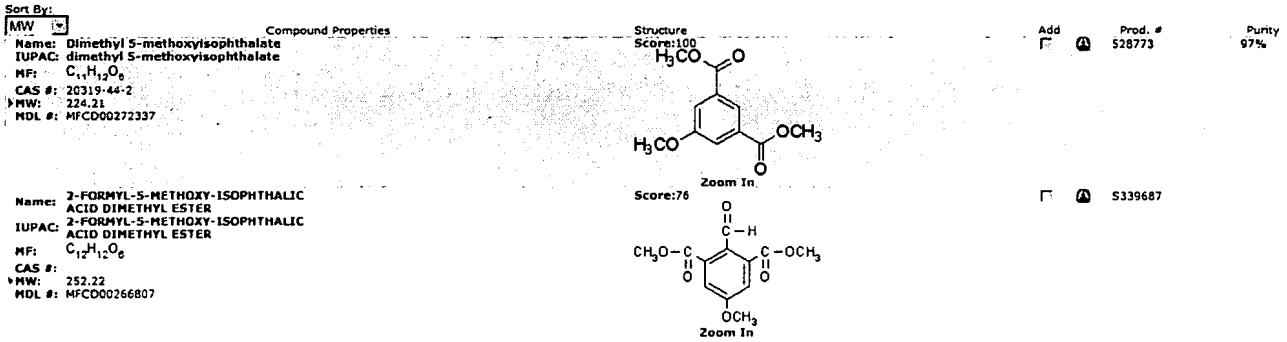
> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

Based on the information given in the specification used to prepare Example 11 (pg. 117 ff.) the synthetic diagram of Scheme 1 was constructed.



Scheme 1. Synthesis of the compounds of the instant invention.

It is clear that compounds bearing the 3-(pyridin-3-yl)-7-azabicyclo[3.3.1]non-2-ene core **IB** and a 3-(pyridin-3-yl)-7-azabicyclo[3.3.1]nonane core **ID** Formula II (Figure 1 where definitions are as above), were prepared. The route available to the compounds is that of Scheme 1. **(F & G)** The key materials needed for this synthesis are a plethora of 5-methoxyisopthalic acids **1** and boronic acids **7**. A search for derivatives of **1** in the Sigma-Aldrich catalog to support the breadth of Zs listed in the instant claims reveals only one:



It seems unlikely that this one will survive the brutal conditions employed (i.e. it will be reduced by $LiALH_4$). It is clear that a route to compounds IA and IC require Cyclohex-3-enyl-nitriles of enormous scope (pg. 130).: It is noted that a synthesis of non-commercial boronic acids **7** was provided, however a seemingly endless array of bromopyridines would be needed. According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction on how to make or where to buy compounds of the type **1. (F)**. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference

materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-yl-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula

The limitations of the chemistry used to prepare the compounds is readily apparent as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually

> implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface. **(E)**

A key step in the formation of the azabicyclo core is the amination of the bismethanesulonate **4** with ammonia and its subsequent protection to yield **5 (Scheme 1). (F & G)** However these reactions are limited by the nature of the substrate, meaning if other electrophilic centers are present (as is claimed they would be aminated). In addition the presence of other nucleophiles would cause the acylation of the groups by ethylchloroformate **(C, E, F & G)** Many of the compounds currently under the Markush claim could not exist but would self-polymerize instantaneously if prepared as stated by Dorwald ibid. pg. 41 "It goes without saying that a compound will decompose or oligomerize if it contains functional groups which can react with each other. Because intramolecular reactions often proceed at much higher rates than their intermolecular variants, functional group incompatibilities may arise unexpectedly, involving groups which would not react intermolecularly..." **(C & E)**

The list of reagents that are incompatable with "substituents" could be discussed at length. Consider $LiAlH_4$ (Scheme E), a very promiscuous reductant indeed that will react with nearly any electrophilic functional group ("Lithium Aluminum Hydride" Paquette, L. in *Encyclopedia of Reagents for Organic Synthesis* Online Posting Date: October 15, 2004 2004 John Wiley & Sons, Ltd. "http://www.mrw.interscience.wiley.com/eros/articles/rl036/frame.html") including esters, azides, nitriles (Amundsen, L.H. et. al. *J. Am. Chem. Soc.* **1951**, *73*, 242-244), etc.

The conversion of **6** and **7** to **8** via the Suzuki-coupling is likewise limited. It is well known in the art that Pd undergoes oxidative addition to "halo" a substituent (readily to I, and Br), which is recited for Z. The applicant's own disclosure is shown as evidence of this fact. One reviewer has made the following statement about Pd-cataylzed cross-couplings:

> The large number of highly diverse examples of high-yielding Pd-catalyzed organic reactions might give the non-specialist the impression that almost any conceivable transformation might work in the presence of a suitable Pd catalyst. This is, of course, not true, and even the most robust Pd-catalyzed processes have their limitations. Some of these will be discussed in the following sections. The most important unwanted processes which can compete with Pd(0)-catalyzed C-C bond formation include homocoupling or reduction of the halide and homocoupling, C-protonation, or oxidation of the organometallic reagent. (Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim Chapter 8, pgs. 279-308.)

Dorwald has numerous references to reactions that do not work. In particular in the instant case the claims are directed to groups that will result in undesired processes that do not lead to the product. When Z is alkyl and ortho to bromo, a variety of cylcometallation process can occur and "give rise to unexpected products or, if the palladacycles are too stable, the catalyst will be consumed and no further reaction will occur." (Dorwald ibid. pgs. 298-299). In addition certain ortho groups will chelate the metal and prevent reaction: "Accordingly, aryl halides with strongly chelating ortho-substituents will undergo transition metal-catalyzed C-C bond formation only sluggishly or not at all." (Dorwald ibid. 300-301). It is also a well known limitation of Pd catalyzed reactions that sterically bulky substituents hinder or completely inhibit the reaction.

While these chemical limitations are significant, perhaps more significantly are the limitations of activity at nAChR. The medicinal chemistry of nAChR is relatively well-developed and many limitations are well known in the art. The compounds of the instant case can be seen as analogs of Epibatidine, whose SAR has been reviewed see F. Ivy Carroll

"Epibatidine structure–activity relationships" *Bioorganic & Medicinal Chemistry Letters* **2004** *14*, 1889–1896.:

> "Conversion of epibatidine to its N–CH3 analogue had only small effects on biological activity, **whereas changes to larger groups or an acetyl group resulted in large losses of activity.** Compounds with biological properties much like epibatidine can be obtained by replacement of the 2'-chloro group with other halogens or a hydrogen, while electron donating group in the 2'-position cause a large reduction in affinity. The addition of 3'-substituents to epibatidine can lead to compounds with high affinity for nAChR that are agonist or mixed agonist-antagonists." **(C & E)**

While of course these compounds have not been made, these scope of the claims are not desirable modification. We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case. **(F & G)** In fact the only information we are given is how to conduct an assay and no actual performance of the compounds in the assay has been revealed (although the octane compounds were tested.) **(F)** What are the important structural features for the claimed utility? We do not know. **(H)** Related 3-pyridyl nAchRs were modeled based on 58 different kinds of compounds and the authors came to following conclusion about substituents on the 3-pyridyl ring:

> "The relative localization of the aromatic nitrogen and the group with heterocycle was important to binding affinity of the pyridyl ethers. The aromatic nitrogen must be located on the meta-site of the group with heterocycle so that it can be act as an effective H-bond donor. **Besides this, the 2-, 4-, 5- and 6-substitute of the pyridine ring all had strong impact on the ligand affinity**. The 2-position of the pyridine ring was likely situated near the positive nitrogen of the heterocycle. Thus, the physicochemical property of the 2-substitute had strong influence on the binding affinity. **The best suitable 2-substitutes should be less bulky steric and/or less negative charged group without H-bond acceptor property.** The 4-postion of pyridine might be localized near the negative residues of the receptor, which demanded 4-substitute should be less negative charged. The 5-

> position seemed oriented toward such a spacious area that a suitable steric bulky group would favor to the increment of the affinity." Huabei Zhang, Hua Li, Qinqin M. "QSAR study of a large set of 3-pyridyl ethers as ligands of the α4β2 nicotinic acetylcholine receptor." *Journal of Molecular Graphics and Modelling* **2007**, *26*, 226–235.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

6. Claims 70 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to complex pharmaceutical compositions with the compounds of the instant claims and compounds described by function "antineoplastic agent", "VEGF inhibitor". The Wands factors are listed above in previous rejection. A few are summarized here: **(F) The amount of direction provided by the inventor:** We have no assays describing the activity of the compounds of the instant case. Are they agonists or antagonists? No evidence of synergism between the cmpounds of the instant case and "antineoplastic agent", "VEGF inhibitor"is presented. **(C) The state of the prior art: (E) The level of predictability in the art:** The prior art teaches that

nicotine may promote tumor growth through this very same receptor Desphande et. al. "Nicotine inhibits apoptosis induced by chemotherapeutic drugs by up-regulating XIAP and survivin" PNAS **2006**, 6332–6337, however other mechanisms are also known including a nicotine mediated beta andrenergic receptor pathway that is distinct. One researcher describes the situation of nicotine this way:

> "It has also been shown to play a role in carcinogenesis through the nicotinic acetylcholine receptors (nAChRs) (Minna, 2003; Schuller et al., 2000; Ye et al., 2004). There are also growing evidences supporting that nicotine may act via b-adrenoceptors (Jin et al., 2004; Park et al., 1995; Schuller et al., 1999). In particular, nicotine suppressed apoptosis of lung cancer cells by stimulating the phosphorylation of B-cell lymphoma 2–associated death promoter protein via the upstream b-adrenoceptors but not the α7-nAChR (Jin et al., 2004). Nicotine has been shown to induce secretion of adrenaline from adrenal glands (Li and Forsberg, 1996; Narita et al., 1973). The other line of evidence also suggests that adrenaline, a b-agonist, plays a contributory role in carcinogenesis and tumor progression (Entschladen et al., 2005). Wong et. al. "Nicotine Promotes Colon Tumor Growth and Angiogenesis through b-Adrenergic Activation" *Toxicological Sciences* **2007**, *97*, 279–287.

Even for nicotine, the mechanism of its tumor promotion is unclear and controversial. The compounds of the instant case have an unknown pharmacology. Are they agonists? Are they like nicotine and promoters of tumor growth? Unknown. Even if they were antagonists, it is unclear that this is correlated with antitumor activity. Moreover the claims require at least one other active compound of unaccertainable scope, however Borisy et. al. "Systematic discovery of multicomponent therapeutics" PNAS **2003**, *100*, 7977–7982.

> "In some instances, a synergistic combination that we, to our knowledge, discovered empirically will have relevant citations in the literature such that it may appear to have been almost predictable with hindsight. **However, many other equivalent predictions would also be made from the literature and these usually do not result in synergy when tested experimentally. In this sense, biological literature contains many anticipatory observations and speculations regarding connections between pathways (and compounds),**

> **most of which do not ultimately prove to be synergistic when tested directly**."

(G) The existence of working examples: No working examples exist; **(H) The quantity of experimentation needed to make or use the invention:** The correlation between the hypothetical synergism between a compound that does not necessarily function, with perhaps billions of compounds ("antineoplastic agent", "VEGF inhibitor") is not shown. The amount of experimentation required approaches the infinite. See Grant R. Zimmermann "Multi-target therapeutics: when the whole is greater than the sum of the parts." *Drug Discovery Today* **2007**, *12*, 34-42.

> "The success of the combination drugs discussed justifies efforts to identify novel multi-target therapeutics early in the discovery process, **but the systematic pursuit of combination drugs presents unique experimental challenges. First, multi-target therapies rely upon complexity in the disease system, which must be reproduced in vitro for discovery screening. Second, without a priori knowledge of target pairs that interact synergistically, the vast space of possible target combinations needs to be covered by an agnostic search. Finally, the sensitivity of synergistic interactions to dosing ratios requires substantial experimental investment and specialized analyses for each combination tested**.....because the number of combinations expands quadratically with the number of agents being tested, multi-target discovery efforts are usually constrained by the efficiency of the screening platform available. For example, **even a small set of 2000 agents generates almost two million unique pairwise combinations**."

It is very clear that undue experimentation is required. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that

one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Conclusion

7. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

8. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
12/12/07